REMARKS

Status of the Claims

Claims 1-5 are pending and under consideration in this application.

Claim Amendments

Claims 1-2 and 4-5 have been amended. Specifically, claims 1-2 and 4-5 have been amended to replace the transition "having a nucleotide sequence of" with the transition "consisting of the nucleotide sequence". Claims 7-10 have been added to recite that the claimed nucleic acids or probe also incorporate "one or more "labels". Support for new claims 7-10 can be found on page 6, lines 7-25 and lines 31-32. No new matter has been added as a result of these amendments.

Brief Summary of the Present Invention

The present invention relates to nucleic acid sequences, methods of using these nucleic acid sequences and kits containing these nucleic acid sequences that are useful for identifying a polymorphism in codon 16 of the ß2-adrenergic receptor gene. Identification of individuals containing a polymorphism in this codon of the ß2-adrenergic receptor gene is very useful. Specifically, it is known that certain medications used to treat asthma might not be as efficacious in individuals containing a polymorphism in this codon of the ß2-adrenergic receptor gene. Thereupon, it is useful for a physician to know whether or not an individual has a polymorphism in codon 16 of his/her ß2-adrenergic receptor gene prior to prescribing medication to said individual for the treatment of asthma.

Specifically, the present invention relates to the use of a combination of nucleic acids, namely a first nucleic acid consisting of the nucleotide sequence of SEQ ID NO. 2 and a second nucleic acid consisting of the nucleotide sequence SEQ ID NO. 3, as primers to amply a nucleic acid sequence comprising the ß2-adrenergic receptor gene. SEQ ID NOs. 2 and 3 amplify both the wild type and

mutant (polymorphic) alleles of the ß2-adrenergic receptor gene. SEQ ID NO. 4 is used as a probe to identify the wild type allele of the human ß2-adrenergic receptor amplification product. SEQ ID NO. 5 is used as a probe that detects the mutant (polymorphic) allele of the ß2-adrenergic receptor amplification product. As shown in Example 2, particularly Table 2, test samples clearly react with only the wild type probe (homozygous wild type – SEQ ID NO. 4), only the mutant probe (homozygous mutant – SEQ ID NO. 5) or both probes (heterozygous – SEQ ID NOs. 4 and 5).

35 U.S.C. §112, First Paragraph Rejection

Claims 1-5 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner rejects claims for encompassing "primers 'having' any 'nucleotide sequences of' SEQ ID NO: 2 or SEQ ID NO: 3" and "probes having any 'nucleotide sequence of' SEQ ID NO: 4 or 5". According to the Examiner, the originally filed specification does not provide basis for the additional molecules that are encompassed by claims as amended (See the Office Action, page 2). Applicants respectfully traverse this rejection.

While not agreeing with the Examiner's rejection, but in order to expedite prosecution, Applicants have amended claims 1-2 and 4-5 to recite nucleic acids "consisting of the nucleotide sequence" rather than "having a nucleotide sequence of" nucleotide sequences. Therefore, in view of these amendments, Applicants submit that this rejection is now moot and should be withdrawn.

35 U.S.C. §102(b) Rejection

The Examiner rejects claims 1-5 as being anticipated under 35 U.S.C. §102(b) in view of Drazen et al (WO 98/39477) ("Drazen et al."). According to the Examiner, "the claims are sufficiently broad so as to encompass any molecule comprising any subsequences of the recited SEQ ID Nos." More specifically, with respect to claims 1-2 and 5, the Examiner says that Drazen et

al. disclose kits comprising primer pairs that specifically amplify 2 different codon 16 variants of the ß2-adrenergic receptor as well as control DNA molecules that include both the variant receptor gene alleles. With respect to claims 3-4, the Examiner says that Drazen et al. disclose allele-specific amplification of a portion of a ß2-adrenergic receptor target gene. Moreover, also with respect to claim 4, the Examiner says that Drazen et al. further disclose amplification of a portion of the ß2-adrenergic receptor gene, followed by allele-specific hybridization to effect detection of a target allele. Applicants respectfully traverse the rejection.

In their SEQ ID NO. 2, Drazen et al. teach the human ß2-adrenergic receptor gene. This gene is 3451 base pairs in length and comprises both of Applicants' SEQ ID NOs. 2 and 3. As explained previously herein, claims 1-2 and 4-5 have been amended to replace the transition "having a nucleotide sequence of" with the transition "consisting of the nucleotide sequence". Thereupon, with these amendments, the claims no longer read on any polynucleotide sequence which contains SEQ ID NOs. 2 or 3. Specifically, SEQ ID NOs. 2 and 3 are each 19 base pairs in length and given their length, are useful as primers for amplifying polymorphisms in the human ß2-adrenergic receptor gene. Drazen et al. do not teach or even suggest nucleic acid sequences having the length of SEQ ID NOs. 2 and 3 or combinations of these nucleic acids. Moreover, Drazen et al. do not teach or suggest nucleic acid sequences having the sequences of SEQ ID NOs. 4 and 5 and that are useful as probes. Accordingly, Drazen et al. do not anticipate claims 1-5.

In view of the aforementioned amendments and arguments, Applicants submit that claims 1-5 are not anticipated by Drazen et al. and that this rejection is now moot and should be withdrawn.

35 U.S.C §103 Rejection

The Examiner rejects claims 1-5 as being obvious over Dewar et al. in view of Drazen et al. and Matalon et al. (U.S. Patent No. 5,679,635) ("Matalon et

al.") for the reasons set forth in the Office Actions mailed on October 11, 2000 and August 25, 2005. Specifically, in the instant Office Action, the Examiner states that she did not rely on Matalon et al. with regard to the ß2-adrenergic receptor gene. According to the Examiner, the reference was only relied on to show the routine nature of selecting and producing suitable probes and primers for use in PCR and allele specific hybridization (See the Office Action of June 29, 2006, pages 5-6). The Examiner states that results obtained by Matalon et al. have no bearing on the patentability of Applicants' claims. Applicants respectfully traverse this rejection. Applicants incorporate herein all of the arguments made in their last Amendment. Moreover, Applicants would like to add the following.

While it is correct that patentability of Applicants' claims does not depend on the results obtained by Matalon et al., Applicants again submit that it is unfair of the Examiner to require Applicants to provide "unexpected" results for novel and unobvious claimed primers and probes in view of the fact that Matalon et al. claimed primers without showing any "unexpected results."

Additionally, the Examiner further states that Applicants' last Amendment did not address the teachings of Dewar et al. and Drazen et al. other than to restate the Examiner's arguments regarding those references. Applicants respectfully disagree. Applicants addressed the Examiner's argument that Dewar et al. and Drazen et al. rendered the claims obvious. The Examiner admits that Applicants' primers and probes are not disclosed in either Dewar et al. or Drazen et al. Applicants submit that neither Dewar et al. nor Drazen et al., alone or in combination disclose or suggest applicants claimed combinations of nucleic acids. Further, Applicants' contend that the design, selection, and production of suitable probes and primers for use in PCR and allele specific hybridization is not routine in the art and this was the main point of Applicants argument in response to the obviousness rejection. As Applicants stated in their last Amendment, Matalon et al. was incorrect in stating that the design and selection of suitable probes and primers is routine. As Applicants argued, all

primer and probe sequences do not function identically, and therefore, selecting effective primers that would hybridize to a known target is not obvious. As Applicants discussed in their last Amendment (see Amendment, re-submitted on March 8, 2006 page 8, second paragraph through page 9, second paragraph):

Applicants submit that primer and probe sequences can be initially selected based on comparisons between known sequences to find conserved regions. However, even when conserved sequences are selected, they do not necessarily work in an amplification reaction. In practice, many primer and probe sequences must be tested in an amplification reaction setting to determine the suitability of the primer or probe sequences for their intended purpose. For example, efficiency of detection is often dependent on the distance between the primers. Specifically, if the primers are too close, a lot of product is obtained which cannot be detected over background (i.e., primer dimers), or there is not enough room for the probe to bind. On the other hand, if the primers are too far from each other, one may obtain little or no product. Additionally, the efficiency of the hybridization is also dependent on the degree of sequence identity between the primer and the target and the reaction condition used (in particular, the annealing or hybridization temperature).

Because there is some variability in the genomic sequences of various ß2 adrenergic receptor isolates, not all primers will detect all targets equally or predictably. If there is a poor match between the primers or probes, one would have to run reactions at various annealing temperatures until the product is detected or include additives to the reaction buffer that improve annealing between mismatched primers and targets. These steps are not at all obvious and require inventive skill. Accordingly, all possible primer and probe sequences are not functionally equivalent and a commercially acceptable efficiency of any primer or probe sequences cannot be predicted with any certainty.

Furthermore, Applicants draw the Examiner's attention to He Q. et al. *Biotechniques*, 17(1): 82-86 (1994), a copy of which is enclosed. This reference details the unexplained difficulties surrounding the selection of primer and probe sequences and indicates that adjusting reaction parameters is not necessarily a means for making primer or probe sequences efficacious. In fact, the reference suggests choosing different primer or probe sequences instead of trying to get an unresponsive set of primers to work by changing reaction conditions. Hence, all primer and probe sequences are not functionally equivalent and selecting alternative primer or probe sequences that can be employed for their intended purpose requires inventive skill and is not obvious.

The Examiner states that she was not persuaded by this reasoning because

Applicants' claims are no longer limited to the specific primers and probes exemplified in the specification, but are rather sufficiently broad so as to encompass a wide variety of primers and probes (see discussion above). Thus, the features upon which Applicants' rely (i.e., the particular primers of SEQ ID NOS 2-3 and probes of SEQ ID Nos 4-5 and the fact that these molecules have been shown to function in the assays described in the specification) are not required by the rejected claim(s) (See Office Action mailed on June 29, 2006, page 6).

As discussed previously herein, Applicants have amended claims 1, 2 and 4-5 to recite nucleic acids "consisting of the nucleotide sequence" rather than "having a nucleotide sequence of" nucleotide sequences. In view of these amendments, Applicants respectfully submit that this rationale no longer holds.

In conclusion, Applicants' primers and probes are not taught in the prior art and it would not have been obvious to a person of ordinary skill in the art how to obtain the claimed primers and probes. Accordingly, in view of the above arguments, Applicants submit that the rejection of claims 1-5 as being obvious over Dewar et al. in view of Drazen et al. and Matalon et al. is improper and should be withdrawn.

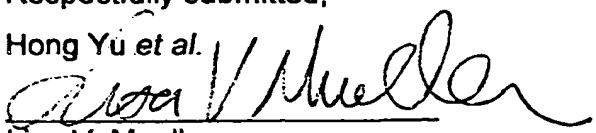
CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 102, 103, and 112. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Hong Yu *et al.*



Lisa V. Mueller
Registration No. 38,978
Attorney for Applicants

Wood, Phillips, Katz, Clark & Mortimer
500 West Madison Street
Suite 3800
Chicago, IL 60662-2511

Tel.: (312) 876-2109
Fax.: (312) 876-2020